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Published in:

Multiple Sclerosis and Related Disorders

DOI:

[10.1016/j.msard.2019.03.005](https://doi.org/10.1016/j.msard.2019.03.005)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:

2019

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

van der Hiele, K., van Gorp, D. A. M., Heerings, M. A. P., Jongen, P. J., van der Klink, J. J. L., Beenakker, E. A. C., van Eijk, J. J. J., Frequin, S. T. F. M., van Geel, B. M., Hengstrnan, G. J. D., Hoitsma, E., Mostere, J. P., Verhagen, W. I. M., de Gans, K., Zemel, D., Middelkoop, H. A. M., & Visser, L. H. (2019). Caregiver strain among life partners of persons with mild disability due to relapsing-remitting multiple sclerosis. *Multiple Sclerosis and Related Disorders*, 31, 5-11. <https://doi.org/10.1016/j.msard.2019.03.005>

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Clinical trial

Caregiver strain among life partners of persons with mild disability due to relapsing-remitting multiple sclerosis

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ARTICLE INFO

Keywords:

Multiple sclerosis
Life partners
Caregiver strain
Neuropsychiatry
Cognition

ABSTRACT

Background: Multiple sclerosis (MS) is a chronic disorder of the central nervous system with an unpredictable disease course. Life partners often become caregivers, which can be both rewarding and challenging, as the caregiver's physical and mental health is often negatively affected. Previous studies on caregiver strain focused on caregivers of persons with MS with relatively high disability levels, while caregiver strain may already be experienced by life partners living with mildly disabled persons with MS.

Objective: The current study examines factors associated with caregiver strain in life partners of persons with mild disability due to relapsing-remitting MS.

Methods: We included 173 persons with relapsing-remitting MS (79% female; mean age 42.8 years; 90% employed; median EDSS 2.0) and their life partners. The life partners completed questionnaires on caregiver strain and neuropsychiatric and cognitive functioning of the person with MS. The persons with MS completed questionnaires about demographics, fatigue, personality, physical, cognitive and neuropsychiatric functioning, and underwent neuropsychological and neurological examinations. A linear regression analysis was conducted to examine predictors of caregiver strain.

Results: 24% of the life partners experienced above average levels of caregiver strain. A multivariate linear regression analysis revealed that a higher age of the person with MS ($\beta = 0.16$, $p = 0.04$), more physical disability ($\beta = 0.17$, $p = 0.04$), more cognitive and neuropsychiatric problems of the person with MS as reported by

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<https://doi.org/10.1016/j.msard.2019.03.005>

Received 10 July 2018; Received in revised form 18 January 2019; Accepted 5 March 2019

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the life partner ($\beta = 0.33, p = 0.001$) and higher severity of neuropsychiatric symptoms as reported by the life partner ($\beta = 0.32, p = 0.001$) were associated with higher caregiver strain ($R^2 = 0.49$).

Conclusion: Higher caregiver strain in life partners of persons with mild disability due to relapsing-remitting MS was primarily associated with cognitive and neuropsychiatric problems of the person with MS.

1. Introduction

Multiple sclerosis (MS) is a disabling disorder of the central nervous system with an unpredictable disease course (National MS Society, 2017). MS is mostly diagnosed in early or middle adulthood, impacting family relations and the building and maintaining of a working career (Buhse, 2008). Life partners often become caregivers and provide daily assistance with personal care, homemaking, mobility, leisure activities and in coping with the disease (Buchanan et al., 2011; Carton et al., 2000). A recent study found that 58% of persons with MS report having at least one caregiver (Katsavos et al., 2017).

Research into positive aspects of caregiving for caregivers is scarce; the few studies that have been done report an increased sensitivity towards another person's needs and problems, companionship and a sense of fulfilment (Cohen et al., 2002; Knight et al., 1997). Other studies have found negative effects of caregiving on the caregiver's physical and mental health, social participation and financial situation (Buchanan et al., 2011; Buhse, 2008; Giordano et al., 2016; McKeown et al., 2003). Aspects of caregiving that were most negatively rated by spouses of persons with MS concerned worries about the future, the time burden involved and the fact that caregiving leads to more restrictions to life and less time available for the rest of the family (Knight et al., 1997).

Several studies examined caregiver and/or care recipient characteristics involved with caregiver strain when providing informal care for a person with MS. From the caregiver's perspective, an increased ability to cope with caregiving and satisfaction with social support were associated with less caregiver strain (Knight et al., 1997), while a higher number of caregiving hours, more restrictions to the caregiver's ability to perform daily activities, higher carer anxiety, low household income and living with the care recipient were associated with higher caregiver strain (Buchanan et al., 2011; Giordano et al., 2016). Studies were inconsistent on whether male or female caregivers experience more strain (Buchanan et al., 2011; Giordano et al., 2016; Knight et al., 1997; Perrin et al., 2015). In terms of characteristics of the person with MS, the most distressing MS symptoms for spousal caregivers were motor problems and gait disturbance, sudden mood changes, the partner upsetting other people, incontinence and pain (Knight et al., 1997). Higher caregiver strain was associated with higher disability of the person with MS (Figved et al., 2007; Katsavos et al., 2017), less activities of daily living without assistance (Chipchase and Lincoln, 2001) and an increased frequency of bladder dysfunction (Buchanan et al., 2011). The patient's age and disease duration have been positively associated with (aspects of) caregiver strain in some studies (Figved et al., 2007; Katsavos et al., 2017) but not in another (Knight et al., 1997). A study in recently diagnosed persons with MS reported that neuropsychiatric symptoms (i.e. depression, delusions, disinhibition, agitation/aggression and irritability) and cognitive impairment (i.e. memory problems and slower information processing speed) contributed to emotional and social distress in caregivers, over and above the effect of physical disability (Figved et al., 2007). The negative effect of everyday memory problems on caregiver strain already became apparent in a study by Chipchase and Lincoln (2001) who were the first to link caregiver strain with measures of cognitive abilities of persons with MS (Chipchase and Lincoln, 2001). Associations between personality traits of the person with MS and caregiver strain have not been previously examined, although caregiver strain may increase when the caregiver believes that the patient's personality has changed (Buhse, 2008).

Many previous studies focused on caregivers of persons with MS with relatively high disability levels, while caregiver strain has not been specifically examined in life partners living with mildly disabled persons with MS. Other types of caregiver strain may then become more prominent, such as changes in personal and family plans and feelings of distress related to the unpredictable nature of MS, while physical strain and sleep disturbance may be experienced less frequently. In terms of characteristics of the person with MS, cognitive and neuropsychiatric problems may become more prominent influencers of caregiver strain than physical disability (Figved et al., 2007).

The objective of the current study was to examine associations between demographic, physical, cognitive, and neuropsychiatric characteristics of persons with relapsing-remitting MS and caregiver strain experienced by their life partners. The persons with MS participated in the MS@Work study, which examines predictors of work participation in relapsing-remitting MS. They were mostly in paid employment and mildly disabled in terms of physical and cognitive functioning, providing us with the unique opportunity to study caregiver strain among life partners of persons with mild disability due to relapsing-remitting MS.

In accordance with the study by Figved et al. (2007) in recently diagnosed patients with MS, we expect to find associations between higher caregiver strain and more cognitive and neuropsychiatric problems, over and above the effects of physical disability. The current study is partly exploratory and included personality traits and fatigue as novel factors. We expect to find associations between higher caregiver strain and higher levels of neuroticism and lower conscientiousness, as high neuroticism has been associated with neuropsychiatric problems in MS and low conscientiousness with both cognitive and neuropsychiatric complications (Benedict et al., 2013). Furthermore, we expect to find associations between higher caregiver strain and more fatigue as was described in a study by Buhse (2008).

We aim to provide unique information about caregiver strain and related factors in life partners of mildly disabled persons with MS. As the caregivers' well-being is extremely important for their continuing role in assisting the person with MS, a (timely) focus on perceived caregiver strain and assistance with their problems may be beneficial for the caregiver's health.

2. Material and methods

2.1. Design and participants

This study recruited persons with MS from 16 MS outpatient clinics in the Netherlands in the context of the MS@Work study, a prospective longitudinal study on work participation in persons with relapsing-remitting MS (van der Hiele et al., 2015). The criteria for inclusion were a diagnosis of relapsing-remitting MS according to the Polman-McDonald criteria 2010 (Polman et al., 2011), 18 years and older and having a paid job or within three years since the last past job. Persons with comorbid psychiatric disorders or substance abuse (diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders-fifth edition (American Psychiatric Association, 2013)), co-morbid neurological disorders, neurological impairment that might interfere with cognitive testing, or unable to speak and/or read Dutch were excluded from the study. A caregiver may be defined as an unpaid person who helps with the physical care or coping with the disease (Hileman et al., 1992). The partner or spouse living with the person with MS often falls within this category. The MS@Work study included 299 persons with MS, of which

222 approached a person close to him or her. We then selected only the spouses and partners living with the person with MS, as these are most likely to be involved with care activities, leaving 173 persons with MS and their life partners.

The study was approved by the Medical Ethical Committee Brabant (NL43098.008.12 1307) and the Board of Directors of the participating MS outpatient clinics. The persons with MS and their life partners provided informed consent.

2.2. Measures

2.2.1. Life partners

The Modified Caregiver Strain Index (MCSI) (Thornton and Travis, 2003) was used to examine caregiver strain from the life partner's point of view. The MCSI provides an extension of the original 13-item Caregiver Strain Index (CSI) developed by Robinson in the early 1980s (Chipchase and Lincoln, 2001). Instead of dichotomous choices ('yes' and 'no') regarding the occurrence of a burdensome situation, the MCSI offers three response options ('never', 'sometimes' and 'always') offering more nuanced answering options as requested by the caregivers. For each of the 13 items of the MCSI, scores ranged from 0 ('never') to 2 ('always'). Total scores ranged from 0 to 26. As no cut-off was published for the MCSI, we based our cut-off on the original CSI of ≥ 7 burdensome situations occurring 'sometimes' or 'always', which represents scores ≥ 1 SD above the mean of the sample in that study (Chipchase and Lincoln, 2001). It should be noted that this cut-off was purely used for descriptive purposes in the current study.

The Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) was used to measure the severity of neuropsychiatric symptoms and the emotional distress caused by the neuropsychiatric symptoms of the person with MS from the life partner's point of view.

The Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ) (Benedict et al., 2003) was used to examine the cognitive and neuropsychiatric functioning of the person with MS from the life partner's point of view.

2.2.2. Persons with MS

2.2.2.1. Neurological examination. The neurological examination included the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) to assess physical disability, the 9-Hole Peg Test (9HP) (Earhart et al., 2011) to assess arm and hand function and the Timed 25-foot walk (TFW) (Kaufman et al., 2000) to examine mobility and leg function.

2.2.2.2. Neuropsychological examination. The neuropsychological examination consisted of tasks representing cognitive domains like memory, processing speed, verbal word fluency, visual spatial processing and higher executive functioning. Most tests are part of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS), a commonly used and valid test battery for detecting cognitive deficits in persons with MS (Benedict et al., 2006). We included additional tests of executive functioning as these are particularly important for independent daily functioning in people with MS.

We used the Paced Auditory Serial Addition Test (3s version) (PASAT) (Gronwall, 1977) and the written version of the Symbol Digit Modalities Test (SDMT) (Smith, 1982) to examine information processing speed and working memory, the Controlled Oral Word Association Test (COWAT) (Benton et al., 1994) and Semantic Category Fluency Test (SCF) (Mulder et al., 2006) to examine word fluency, the Judgment of Line Orientation Test (JLO) (Benton et al., 1994) to assess visuospatial processing, the Rey Verbal Learning Test (RVLT) (Brand, 1985; Rey, 1958) and Brief Visuospatial Memory Test-Revised (BVMTR) (Benedict et al., 1996) to examine learning and memory capacities, and the Trail Making Test (TMT) (Reitan, 1956) and the Design Fluency (DF) and Colour Word Interference (CWI) subtests of the Delis-Kaplan Executive Function System (Delis et al., 2004) to examine executive

functioning. The TMT B-A index was used as it removes the influence of psychomotor speed and provides a purer measure of executive control as compared with the direct scores, i.e. time needed to complete part A and B (Lezak et al., 2004).

2.2.2.3. Questionnaires. A general questionnaire was used to inquire about demographic characteristics and work participation. The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) was used to assess symptoms of anxiety and depression, the Modified Fatigue Impact Scale-20 (MFIS) (Kos et al., 2003) to determine the physical, psychosocial and cognitive impact of fatigue, the MSNQ (Benedict et al., 2003) to examine cognitive and neuropsychiatric functioning and the NEO Five-Factor Personality Inventory (NEO-FFI) (Hoekstra et al., 1996) to assess the extent to which the personality traits of neuroticism, extraversion, openness, agreeableness and conscientiousness are present.

2.3. Statistical analyses

Our main research aim is to examine associations between characteristics of the person with MS and caregiver strain experienced by their life partners. To this end, we first conducted univariate analyses (Spearman rank correlation analyses and Mann–Whitney *U* tests) to identify characteristics of interest. The variables that were significantly associated with caregiver strain were then included in a multivariate linear regression analysis to examine which characteristics were primarily and independently associated with caregiver strain:

Using Spearman rank correlation analysis, we examined correlations between the level of caregiver strain (MCSI) and the demographic characteristics (age, education), neurological functioning (EDSS, 9HP, TFW), cognitive functioning (PASAT, SDMT, COWAT, SCF, JLO, RVLT, BVMTR, TMT, DF, CWI), neuropsychiatric functioning (HADS depression and anxiety, NPI), cognitive and neuropsychiatric functioning (MSNQ), fatigue (MFIS) and personality (NEO-FFI) of the person with MS. Mann–Whitney *U* tests were then performed to examine differences in caregiver strain in the care recipients' gender and employment status. Variables that were significantly associated with the MCSI at $p \leq 0.05$ were entered as independent variables in a multivariate linear regression analysis (with bootstrapping) with the MCSI as a dependent variable. p values ≤ 0.05 were considered statistically significant. SPSS for Windows (release 23.0) was used for data analysis.

3. Results

3.1. Participants

We included 173 persons with MS and their life partners, i.e., 123 spouses and 50 partners living with the person with MS. The median level of caregiver strain was 4.0, with scores ranging from 0 to 21. For descriptive purposes we used a cut-off of ≥ 7 burdensome situations occurring 'sometimes' or 'always'. Based on this cut-off 24% of the life partners showed above average levels of caregiver strain. The three types of caregiver strain most frequently experienced were other demands on the caregiver's time, the need to make changes in personal plans and the need to make family changes. Physical strain, feeling overwhelmed and work adjustments were experienced least often.

The three most common neuropsychiatric symptoms present in the persons with MS, as reported by the life partners, are irritability/lability (38%), depression (28%) and appetite disturbance (22%). The highest mean caregiver distress scores are reported for agitation/aggression, disinhibition, depression and anxiety. The characteristics of the 173 persons with MS can be found in Tables 1–4.

Table 1
Demographic characteristics of the persons with MS ($N = 173$).

	Mean (SD)	Median (IQR)	N (%) or min–max
Female			136 (78.6%)
Age, years	42.8 (8.6)		24–60
Educational level		4.0 (2.0)	2–8
Having a paid job			155 (89.6%)

Means (SD) and medians (IQR) were noted respectively for variables with parametric and non-parametric data distributions.

SD, Standard Deviation; IQR, Interquartile Range; Educational level ranges from 1 (up to six years of primary education) to 8 (postdoctoral).

Table 2
Neurological functioning of the persons with MS ($N = 173$).

	Median (IQR)	Min–max
EDSS	2.0 (1.3)	0–6
9HP, time in s	20.0 (4.0)	10–57
TFW, time in s	5.6 (1.3)	3–16
Disease duration in years	5.0 (9.0)	0–26

Medians (IQR) were noted as the variables had a non-parametric data distribution.

IQR, Interquartile Range; EDSS, Expanded Disability Status Scale; 9HP, 9-Hole Peg Test; TFW, timed 25-foot walk.

3.2. Univariate relations between caregiver strain and characteristics of the persons with MS

To identify characteristics of the persons with MS significantly associated with caregiver strain to be included in the multivariate analysis, we examined correlations between caregiver strain and demographic and clinical characteristics of the persons with MS (Table 5) and examined whether caregiver strain differs depending on the gender and employment status of the person with MS. We found significant correlations between a higher level of caregiver strain and the persons' demographic characteristics (higher age), neurological functioning (more physical disability and decreased mobility and leg function), cognitive functioning (lower information processing speed), decreased cognitive and neuropsychiatric functioning as reported by the person with MS and the life partner, more neuropsychiatric symptoms and fatigue (more symptoms of depression and anxiety, higher severity of neuropsychiatric symptoms as reported by the life partner and more fatigue) and personality (higher neuroticism and lower

Table 4
Neuropsychiatric functioning, fatigue and personality traits of the persons with MS ($N = 173$).

	Mean (SD)	Median (IQR)	Min–max
HADS depression		3.0 (4.0)	0–15
HADS anxiety		5.0 (5.0)	1–16
NPI severity – life partner reported		2.0 (4.0)	0–18
MFIS, total score	37.1 (15.4)		0–80
NEO-FFI neuroticism	29.1 (7.7)		13–48
NEO-FFI extraversion	40.9 (6.3)		24–58
NEO-FFI openness		36.0 (8.0)	22–56
NEO-FFI agreeableness		46.0 (5.0)	33–54
NEO-FFI conscientiousness	46.3 (5.3)		28–60

Means (SD) and medians (IQR) were noted respectively for variables with parametric and non-parametric data distributions.

SD, Standard Deviation; IQR, Interquartile Range; HADS, Hospital Anxiety and Depression Scale; NPI: Neuropsychiatric Inventory; MFIS, Modified Fatigue Impact Scale; NEO-FFI, NEO Five-Factor Personality Inventory.

conscientiousness). The level of caregiver strain did not differ between life partners of male or female persons with MS ($U = 2366$, $p = 0.58$). Life partners of persons with MS without a paid job experienced higher levels of strain than life partners of those with a paid job ($U = 672$, $p < 0.001$). Based on these findings, we can confirm the hypothesized association between higher caregiver strain on the one hand and higher neuroticism, lower conscientiousness and more fatigue on the other hand.

3.3. Multivariate regression model of caregiver strain

Characteristics of the persons with MS that were significantly associated with caregiver strain at $p \leq 0.05$ in the univariate analyses were entered as independent variables in a multivariate linear regression model for caregiver strain. The multivariate linear regression model ($F(df) = 10.1(13)$, $p < 0.001$) revealed that a higher patient's age, more physical disability (EDSS), more cognitive and neuropsychiatric problems as reported by the life partner (MSNQ – life partner reported) and a higher severity of neuropsychiatric problems as reported by the life partner (NPI total severity – life partner reported) were independently associated with higher caregiver strain (Table 6). Based on these findings, we can confirm the hypothesized association between higher caregiver strain on the one hand and more cognitive and neuropsychiatric problems on the other hand. Contrary to our expectations, physical disability remained a significant, but less

Table 3
Cognitive functioning of the persons with MS ($N = 173$).

	Mean (SD)	Median (IQR)	N (%) or min–max
PASAT 3.0s version, correct		50.5 (11.0)	6–60
SDMT, correct	53.8 (8.9)		33–75
COWAT, total correct	40.3 (12.5)		12–84
SCF, total correct	42.5 (8.4)		21–69
JLO, total correct		26.5 (6.0)	9–30
RVLT, total correct learning trials 1–5		51.0 (13.0)	24–68
RVLT, total correct delayed recall		11.0 (5.0)	2–15
BVMT-R, total correct learning trials 1–3		28.0 (8.0)	12–36
BVMT-R, total correct delayed recall		11.0 (2.0)	5–12
TMT, time in s trails B-A		26.0 (16.9)	–5–125
DF, total correct	34.7 (6.0)		
CWI, time in s card 3 + 4 minus card 1 + 2		53.2 (17.0)	20–173
MSNQ – patient reported	22.2 (9.6)		1–50
MSNQ – life partner reported		17.0 (11.0)	0–34

Means (SD) and medians (IQR) were noted respectively for variables with parametric and non-parametric data distributions.

SD, Standard Deviation; IQR, Interquartile Range; PASAT, Paced Auditory Serial Addition Test; SDMT, Symbol Digit Modalities Test; COWAT, Controlled Oral Word Association Test; SCF, Semantic Category Fluency Test; JLO, Judgement of Line Orientation Test; RVLT, Rey Verbal Learning Test; BVMT-R, Brief Visuospatial Memory Test-Revised; TMT, Trail Making Test; DF, Design Fluency Test; CWI, Colour Word Interference Test; MSNQ, Multiple Sclerosis Neuropsychological Screening Questionnaire.

Table 5

Spearman correlations between caregiver strain and demographic and clinical characteristics of the persons with MS.

Characteristic of persons with MS	Caregiver strain (MCSI) Spearman's rho	p
Age	0.21	0.007**
Educational level	−0.03	0.74
EDSS	0.33	<0.001**
9HP	−0.003	0.97
TFW	0.25	0.002**
Disease duration in years	−0.01	0.86
PASAT 3.0s version	−0.03	0.74
SDMT	−0.16	0.04*
COWAT	−0.10	0.19
SCF	−0.15	0.053
JLO	−0.13	0.11
RVLT learning	−0.04	0.61
RVLT delayed recall	0.03	0.73
BVMT-R learning	0.01	0.86
BVMT-R delayed recall	−0.06	0.48
TMT trails B-A	0.03	0.71
DF	−0.01	0.88
CWI	0.002	0.98
MSNQ – patient reported	0.25	0.001**
MSNQ – life partner reported	0.48	<0.001**
HADS depression	0.29	<0.001**
HADS anxiety	0.20	0.007**
NPI total severity – life partner reported	0.44	<0.001**
MFIS	0.37	<0.001**
NEO-FFI neuroticism	0.19	0.014*
NEO-FFI extraversion	−0.09	0.23
NEO-FFI openness	0.02	0.77
NEO-FFI agreeableness	−0.04	0.58
NEO-FFI conscientiousness	−0.20	0.007**

MCSI, Modified Caregiver Strain Index; EDSS, Expanded Disability Status Scale; 9HP, 9-Hole Peg Test; TFW, timed 25-foot walk; PASAT, Paced Auditory Serial Addition Test; SDMT, Symbol Digit Modalities Test; COWAT, Controlled Oral Word Association Test; SCF, Semantic Category Fluency Test; JLO, Judgement of Line Orientation Test; RVLT, Rey Verbal Learning Test; BVMT-R, Brief Visuospatial Memory Test-Revised; TMT, Trail Making Test; DF, Design Fluency Test; CWI, Colour Word Interference Test; MSNQ, Multiple Sclerosis Neuropsychological Screening Questionnaire; HADS, Hospital Anxiety and Depression Scale; NPI, Neuropsychiatric Inventory; MFIS, Modified Fatigue Impact Scale; NEO-FFI, NEO Five-Factor Personality Inventory.

* $p \leq 0.05$.

** $p \leq 0.01$.

influential, independent predictor of caregiver strain.

4. Discussion

The current study examined associations between caregiver strain experienced by life partners of persons with mild disability due to relapsing-remitting MS. We found that caregiver strain is not uncommon and that higher caregiver strain in life partners of persons with mild disability due to relapsing-remitting MS was primarily associated with cognitive and neuropsychiatric problems of the person with MS as reported by the life partner.

4.1. Caregiver strain

Twenty-four percent of the life partners experienced above average caregiver strain. Although this is lower than the respectively 42% and 46% strained caregivers found in previous studies (Chipchase and Lincoln, 2001; Khan et al., 2007), the percentage seems relatively high when considering that the persons with MS were mildly disabled and mostly had paid work.

The three types of caregiver strain most frequently experienced were other demands on the caregiver's time, the need to make changes in personal plans and the need to make family changes. These aspects,

Table 6

Results of the multivariate regression analysis for caregiver strain. Confidence intervals, standard errors and p values for the multivariate regression analyses are based on 1000 bootstrap samples.

Caregiver strain	B (S.E.)	Beta	CI	p value
Constant	3.33 (4.23)		−4.24–11.04	0.46
Age	0.07 (0.03)	0.16	0.01–0.13	0.04*
EDSS	0.51 (0.25)	0.17	0.04–0.88	0.04*
TFW	−0.20 (0.21)	−0.07	−0.70–0.37	0.29
SDMT	0.00 (0.03)	0.001	−0.05–0.05	0.995
MSNQ – patient reported	−0.05 (0.04)	−0.12	−0.13–0.04	0.22
MSNQ – life partner reported	0.13 (0.03)	0.33	0.07–0.19	0.001*
HADS – depression	0.08 (0.13)	0.06	−0.17–0.37	0.54
HADS – anxiety	0.14 (0.15)	0.11	−0.18–0.42	0.37
NPI total severity– life partner reported	0.36 (0.09)	0.32	0.20–0.50	0.001*
NEO-FFI neuroticism	−0.07 (0.04)	−0.14	−0.16–0.02	0.11
NEO-FFI conscientiousness	−0.06 (0.05)	−0.08	−0.18–0.07	0.26
MFIS	0.02 (0.02)	0.09	−0.02–0.08	0.31
Having a paid job	−1.15 (1.09)	−0.09	−3.6–1.05	0.27

$R^2 = 0.49$; $N = 151$.

EDSS, Expanded Disability Status Scale; TFW, timed 25-foot walk; SDMT, Symbol Digit Modalities Test; MSNQ, Multiple Sclerosis Neuropsychological Screening Questionnaire; HADS, Hospital Anxiety and Depression Scale; NPI, Neuropsychiatric Inventory; NEO-FFI, NEO Five-Factor Personality Inventory; MFIS, Modified Fatigue Impact Scale.

* $p \leq 0.05$.

specifically the demands on the caregiver's time and the need to make changes in plans were previously reported (Chipchase and Lincoln, 2001; Knight et al., 1997). They may be considered the initial strains felt by life partners living with a mildly disabled person with MS, while physical strain and feeling overwhelmed are much less common in this stage.

4.2. Univariate relations between caregiver strain and characteristics of the persons with MS

We found several weak to moderate univariate associations between strain experienced by the life partner and the characteristics of the persons with MS. A higher level of caregiver strain was associated with a higher age, more physical disability, decreased mobility and leg function, lower information processing speed, worse cognitive and neuropsychiatric functioning as reported by the person with MS and the life partner, more symptoms of depression and anxiety, higher severity of neuropsychiatric symptoms as reported by the life partner, more fatigue, higher neuroticism, lower conscientiousness and not having a paid job. Most of these factors have previously been associated with caregiver strain in caregivers of persons with MS (Chipchase and Lincoln, 2001; Figved et al., 2007; Katsavos et al., 2017; Khan et al., 2007). An additional interesting finding is that the personality of the person with MS (i.e. higher neuroticism and lower conscientiousness) and higher fatigue were associated with higher caregiver strain. Neither personality nor fatigue emerged as significant independent predictors of caregiver strain in the multivariate model. Personality may be indirectly related to caregiver strain as higher neuroticism and lower conscientiousness have both been associated with neuropsychiatric complications in MS (Benedict et al., 2013). Fatigue may become more influential as its impact on daily life increases. The invisible and unpredictable nature of MS-related fatigue may be difficult to understand for the significant other, but does have an enormous impact on daily life and activities that can be undertaken (Buhse, 2008). Life partners of

persons with a paid job experienced less strain, but this may be related to the better physical, cognitive and psychological health associated with having a paid job (Raggi et al., 2016).

4.3. Multivariate regression model of caregiver strain

When considering the relative contribution of the characteristics of the persons with MS associated with caregiver strain, we found that higher caregiver strain was particularly associated with a higher age of the person with MS, more physical disability, more cognitive and neuropsychiatric problems and a higher severity of neuropsychiatric symptoms as reported by the life partner. Our study thereby confirms previous reports of positive associations between caregiver strain and the age (Figved et al., 2007; Katsavos et al., 2017) and level of physical disability of the person with MS (Chipchase and Lincoln, 2001; Figved et al., 2007; Katsavos et al., 2017). As life partners may be of similar age, the found association between caregiver strain and age may also indicate that older caregivers experience more strain. Cognitive and neuropsychiatric functioning of the person with MS, as perceived by the life partner, explained most variance in caregiver strain. The association between caregiver strain and neuropsychiatric functioning has been previously observed in a study including caregivers of persons with recently diagnosed MS (Figved et al., 2007). We found that agitation/aggression, disinhibition, depression and anxiety were considered most emotionally disturbing for the life partners. As noted by Figved et al. (2007) symptoms such as agitation/aggression and disinhibition are associated with socially unacceptable behaviour and are often difficult to manage, which may subsequently lead to avoidance of social situations and changes in personal and family plans (Figved et al., 2007). Depression and anxiety were reported by the life partner to be present in respectively 28% and 7% of the persons with MS in the current sample. Depression and anxiety are common neuropsychiatric symptoms in MS and have previously been associated with higher caregiver distress (Arnett et al., 2008; Figved et al., 2007; Janssens et al., 2006; Khan et al., 2007; Knight et al., 1997). It seems intuitive that mood disturbances in the person with MS and the associated loss of energy, loss of initiative and worries about the future lead to higher caregiver strain.

In addition, worse cognitive functioning as reported by the life partner was predictive of higher caregiver strain. Previous studies found similar associations between cognitive functioning, i.e. decreased information processing speed, dementia and everyday memory problems, and reduced quality of life and distress in caregivers (Chipchase and Lincoln, 2001; Figved et al., 2007). It should be noted that our model favoured the life partner's perception of cognitive and neuropsychiatric functioning over actual cognitive test performance and patient-reported neuropsychiatric functioning in the prediction of caregiver strain. It seems logical that the life partner's perceptions may be more important than the patient's actual cognitive performance or the patient's own perception of neuropsychiatric functioning in creating caregiver strain. In addition, caregivers may already be aware of subtle changes in memory and information processing before these become evident on cognitive tests. The fact that caregivers may not be able to rely on their partner with MS due to (perceived) memory problems may have led to pressure and a loss of patience, thereby increasing caregiver strain (Chipchase and Lincoln, 2001).

4.4. Strengths and limitations

Strengths of the current study include a large sample of 173 persons with MS and their life partners and the use of a wide range of characteristics of the persons with MS as possible predictors of caregiver strain, including demographic, neurological, cognitive and neuropsychiatric variables. A limitation is that the MS@Work study specifically recruited persons with relapsing-remitting MS with a current or recent paid job. The current study is therefore not representative for the

entire MS population, but does provide unique information about caregiver strain in life partners of persons with mild disability due to relapsing-remitting MS. Our findings imply that it is important to identify caregiver strain in life partners of persons with MS, even in mild cases of MS, and to offer them appropriate information and care. In fact, the persons with MS in the current sample might not describe their life partners as 'caregivers' and the life partners might not see themselves as caregivers. However, when we define a caregiver as an unpaid person who helps with the physical care or coping with the disease, the partner or spouse often falls within this category (Hileman et al., 1992). Another limitation is that the study did not include another patient-life partner sample or a normal life partner sample for comparison. We can therefore not draw any conclusions about the magnitude of caregiver strain or whether the found relations are unique for life partners of persons with MS. In addition, we did not assess the quality of the relationship between the person with MS and their life partner. Previous research shows that perceptions of inequality in the relationship increases the risk of burnout in life partners (Ybema et al., 2002). In previous research on caregiver strain many different measures of caregiver strain or quality of life were used, making it difficult to compare outcomes. These measures include the Zarit Burden Interview (Giordano et al., 2016), General Health Questionnaire (Figved et al., 2007), Neuropsychiatric Inventory distress scale (Figved et al., 2007), Caregiver Strain Index (Chipchase and Lincoln, 2001; Khan et al., 2007), Care Burden Scale (Knight et al., 1997), Palliative Care Outcome Scale-Symptoms-MS (Giordano et al., 2016), caregiver self-reported burden of care (Khan et al., 2007) and a 5-point Likert item for caregiver burden (Buchanan et al., 2011). In the current study we used the Modified Caregiver Strain Index, which provides a useful method for detecting strain levels among informal caregivers (Thornton and Travis, 2003). A clear cut-off score was however not available. For descriptive purposes we therefore employed the cut-off score used in the original Caregiver Strain Index. As caregivers may more easily respond with a middle response category as opposed to a dichotomous 'yes' or 'no' this cut-off should be regarded with caution and seen as exploratory. As already noted by McKeown et al. (2003) there still seems to be a need for an MS specific instrument to assess caregiver strain (McKeown et al., 2003). A final limitation is that, due to the focus of the current study on characteristics of the persons with MS, we were not able to examine the impact of the life partner's characteristics on their level of caregiver strain. It would be interesting to further study the association between the life partner's emotional functioning and the level of caregiver strain experienced when living with a mildly disabled person with MS.

4.5. Conclusions

Many life partners of persons with mild disability due to relapsing-remitting MS, of whom the majority works, experience caregiver strain. In this disease stage caregiver strain is primarily associated with cognitive and neuropsychiatric problems as reported by the caregiver, above the effects of physical disability and age. Our findings highlight the importance of early identification and treatment of cognitive and neuropsychiatric problems in persons with MS. As the caregivers' well-being is extremely important for their continuing role in assisting the person with MS, it is important to routinely assess caregiver strain in life partners of persons with MS, to create awareness of caregiver strain and to offer caregivers information and access to services and support offered by community organizations.

Conflict of interest

Karin van der Hiele received honoraria for consultancies, presentations and advisory boards from Sanofi Genzyme and Merck Serono. Dennis van Gorp received honoraria for presentations from Sanofi Genzyme. Peter Jongen received honoraria from Bayer, Merck

Serono and Teva for contributions to symposia as a speaker or for educational or consultancy activities. Jeroen van Eijk received honoraria for lectures, travel grants and honoraria for advisory boards from Teva, Merck Serono, Sanofi Genzyme, Biogen, Roche and Novartis. Stephan Frequin received honoraria for lectures, grants for research, and advisory boards from Teva, Merck Serono, Sanofi Genzyme, Biogen, Novartis, and Roche. Gerald Hengstman reports grants and personal fees from Biogen, Novartis, Teva, Merck Serono, and Sanofi Genzyme. Elske Hoitsma reports honoraria for lectures, travel grants and honoraria for advisory boards from Novartis, TEVA, Roche, Merck Serono, Sanofi Genzyme, Biogen Idec and Bayer. Jop Mostert reports personal fees from Novartis, Merck Serono, Sanofi Genzyme and Teva. Wim Verhagen received honoraria for lectures from Biogen and Merck Serono, reimbursement for hospitality from Biogen, Teva, Sanofi Genzyme and Merck Serono, and honoraria for advisory boards from Merck Serono. Désirée Zemel received honoraria for advisory boards from Novartis, Merck Serono, Sanofi Genzyme and Biogen. Leo Visser received honoraria for lectures, grants for research and honoraria for advisory boards from Sanofi Genzyme, Merck Serono, Novartis and Teva. The other authors (Marco Heerings, Jac van der Klink, Martijn Beenakker, Björn van Geel, Koen de Gans, Huub Middelkoop) declare that they have no competing interests.

Funding

This work was supported by the National Multiple Sclerosis Foundation, Teva Pharmaceuticals and ZonMw (TOP Grant, project number: 842003003). The funding sources had no role in study design, data collection, data analysis, data interpretation, report writing or decision to submit the article for publication.

Data statement

Data will be made available upon request to the corresponding author.

Acknowledgements

We thank the MS (research) nurses, psychologists and other healthcare professionals involved with data acquisition. We thank I. van Lieshout for her advice on the study design. We are grateful to E.P.J. Arnoldus, H.M. Bos, J. Fermont, R.M.M. Hupperts, P.H.M. Pop and J.W.B. Moll for their help with recruiting participants and acquiring neurological data.

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